PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 4-32344A/CHL	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/02029	International filing date *(day/month/year)* 27.02.2003	Priority date *(day/month/year)* 28.02.2002
International Patent Classification (IPC) or both national classification and IPC A61K45/06		
Applicant NOVARTIS AG		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
30.08.2003	17.06.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Pacreu Largo, M Telephone No. +49 89 2399-7851

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/02029

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-32 as originally filed

Claims, Numbers

1-16 received on 27.04.2004 with letter of 26.04.2004

Drawings, Sheets

1/4-4/4 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 12-16 (in respect of industrial applicability)

   because:

   ☒ the said international application, or the said claims Nos. 12-16 (I.A.) relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	4,5,9,10
	No:	Claims	1-3,6-8,11-16
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-16
Industrial applicability (IA)	Yes:	Claims	1-11
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 12-16 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with to respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. The documents cited in the International Search Report (ISR) are consecutively numbered D1-D9 in the order of their listing. If not indicated otherwise, reference is made to the passages cited in said ISR.

2. Document D1 describes the use of combinations of STI571 with 2 or 3 antineoplastic agents (Ara-C plus Apo2L/TRAIL or Ara-C plus Apo2L/TRAIL plus IFN) in leukemic blasts.

   Document D2 also refers to the use of a combination comprising STI571 + A490 + FTI to treat chronic myeloid leukaemia (CLM).

   Document D3 refers to an ongoing phase II study aiming the treatment of CLM comprising the co-administration of imatinib mesylate (another name for STI571), idarubicine and ara-C.

   Thus, the subject-matter of claims 1-3, 6-8 und 11-16 does not appear to be novel, Art. 33(2) PCT.

3. The subject-matter of claims 4, 5, 9 and 10 appears to be novel, Art. 33(2) PCT since none of the documents of the search report disclose neither a combination comprising STI571, fludarabine and ara-C nor a combination with the four following compounds: STI571, fludarabine, idarubicine and ara-C.

4. However, the subject-matter of claims 4, 5, 9 and 10 does not appear to involve an inventive step for the following reasons:

In general it is not considered inventive to combine two or more active agents for treating a particular disease in the case where said two or more agents are known to be therapeutically effective alone in treating said particular disease. In this regard, it would normally be expected that such a combination of active agents would be more effective than either active agent alone. Exceptions to this general principle may be made if the new combination has a surprising property, e.g. a synergistic therapeutic benefit.

Synergistic activities have already been reported for STI571 in combination with ara-C in *in vitro* studies (see D4 and D5).

The applicant has only shown that the combination STI571 + fludarabine + ara-C is synergistic over the combination fludarabine + ara-C in leukaemic cell lines.

In order to acknowledge an inventive step, a synergistic effect of the triple combination over the combination pairs STI571 + ara-C and STI571 + fludarabine should also be shown.

No data about the effects of a combination of the 4 compounds of claims 5 and 10 can be found in the application.

5. For the assessment of the present claims 12 to 16 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Amended Claims:

1. A combination of (a) an ATP-competitive inhibitor of c-abl kinase activity and (b) with (b) two or more other antineoplastic agents for simultaneous, separate or sequential use.

2. The combination according to claim 1 where the ATP-competitive inhibitor of c-abl kinase activity (a) is N-{5-[4-(4-methyl-piperazino-methyl)-benzoylamido]-2-methylphenyl}-4-(3-pyridyl)-2-pyrimidine-amine, or a pharmaceutically acceptable salt thereof.

3. The combination according to claim 2 wherein (b) the two or more antineoplastic agents are selected from pyrimidine or purine nucleoside analogs and topoisomerase II inhibitors which are independently present in free form or as pharmaceutically acceptable salts.

4. The combination according to claim 3 wherein (b) the two antineoplastic agents are Fludarabine and ara-C which are independently of each other present in free form or as pharmaceutically acceptable salts.

5. The combination according to claim 3 wherein three antineoplastic agents (b) are present in the combination, which are from fludarabine, idarubicine and ara-C which are independently being present in free form or as pharmaceutically acceptable salts.

6. Use of the combination according to any one of claims 1 to 5 for the preparation of a medicament for the treatment of a proliferative disease.

7. Use of the combination according to claim 6 wherein the proliferative disease is leukemia.

8. A pharmaceutical composition comprising a combination of (a) an ATP-competitive inhibitor of c-abl kinase activity with (b) two or more other antineoplastic agents and optionally at least one pharmaceutically acceptable carrier.

9. The pharmaceutical composition according to claim 8 wherein component (a) is (N-{5-[4-(4-methyl-piperazino-methyl)-benzoylamido]-2-methylphenyl}-4-(3-pyridyl)-2-pyrimidine-amine or a pharmaceutically acceptable salt thereof, and (b) are two

Fludarabine and ara-C which are independently of each other present in free form or as pharmaceutically acceptable salts.

10. The pharmaceutical composition according to claim 8 wherein component (a) is (N-{5-[4-(4-methyl-piperazino-methyl)-benzoylamido]-2-methylphenyl}-4-(3-pyridyl)-2-pyrimidine-amine or a pharmaceutically acceptable salt thereof, and (b) are Idarubicine, Fludarabine and ara-C which are independently of each other present in free form or as pharmaceutically acceptable salts.

11. A commercial package comprising (a) an ATP-competitive inhibitor of c-abl kinase activity and (b) two or more other antineoplastic agents, where the active compounds falling under (a) and/or (b) are independently of each other in free form or in the form of pharmaceutically acceptable salts, for simultaneous, chronically staggered or separate use in the delay of progression or treatment of a proliferative disease.

12. A method of treating a warm-blooded animal suffering from a proliferative disease, comprising administering to said animal a combination which comprises (a) an ATP-competitive inhibitor of c-abl kinase activity and (b) two or more other antineoplastic agents, where the active compounds falling under (a) and/or (b) are independently of each other in free form or in the form of pharmaceutically acceptable salts, in a dose that is pharmaceutically effective in the treatment of said disease.

13. The method according to claim 12 where component (a) is (N-{5-[4-(4-methyl-piperazino-methyl)-benzoylamido]-2-methylphenyl}-4-(3-pyridyl)-2-pyrimidine-amine, or a pharmaceutically acceptable salt thereof.

14. The method according to claim 12 where component (a) is N-{5-[4-(4-methyl-piperazino-methyl)-benzoylamido]-2-methylphenyl}-4-(3-pyridyl)-2-pyrimidine-amine, or a pharmaceutically acceptable salt thereof, and component (b) is a combination of two or more of the compounds selected from purine nucleoside analogs and topoisomerase II inhibitors, independently in free form or as pharmaceutically acceptable salts.

15. The method according to claim 12 where component (a) is N-{5-[4-(4-methyl-piperazino-methyl)-benzoylamido]-2-methylphenyl}-4-(3-pyridyl)-2-pyrimidine-amine, or a pharmaceutically acceptable salt thereof, and component (b) includes two or more of the compounds selected from Idarubicine, Fludarabine and ara-C which are

independently of each other present in free form or as pharmaceutically acceptable salts.

16. The method according to claim 12 where the proliferative disease is a leukaemia